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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,313	06/03/2002	Michael Hallek	50125/044001	5985

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,313	HALLEK ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed January 31, 2005 is acknowledged and entered. All objections and rejections under 35 U.S.C. 112, second paragraph, and 35 U.S.C. 102(b) of the previously pending and elected claims 72-73 are moot in view of Applicant's cancellation of claims 72-73. New claims 74-93 are pending. Claims 74-93 are under examination because they are drawn to the same subject matter that was previously under examination.

Oath/Declaration

2. In the previous Office action of November 8, 2004, the form PTOL-326 indicated that the oath/declaration was objected to, however, the Office action did not explain the supposed deficiency. It is apparent from the 371-acceptance letter mailed to Applicant on October 15, 2002, that an oath/declaration was filed subsequent to the un-executed declaration filed January 15, 2002. This document has not been found in the file. Applicant is requested to submit another copy of the signed oath/declaration. Any inconvenience is regretted.

Claim Rejections - 35 USC § 112

3. Claims 74-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The term "negligible reduction in the infectivity of the virus" in claim 74 and dependent claims 75-93 is a relative term which renders the claim indefinite. The term "negligible" is not defined by the claim, the specification does not provide a standard for ascertaining

the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given this relative terminology that is subject to individual interpretation, the metes and bounds of the claims cannot be determined.

- Claim 75 is indefinite because it is unclear whether the claim is referring to viral particle formation, or some other structural particle formation.
- Claim 77 is indefinite because of the phrases, "derived from" and "derived therefrom". The term "derived" indicates that the product, in this case a virus, has been modified such that only part of the original virus remains. Neither the claims nor the specification define what part of the derived virus is retained from the original. The metes and bounds of the claims are not clear without a explanation of what the derived virus retains. It is suggested that Applicant remove the terms "derived from" and "derived therefrom" in order to overcome this rejection.
- Claim 80 is indefinite for the use relative terminology, "high or low molecular weight compound(s)". This phrase is indefinite because the terms "high" and "low" lack comparative basis and are subject to individual interpretation. The metes and bounds of the molecular weight compound cannot be determined based on the terms "high" and "low".
- Claim 84 is indefinite because of the phrase, "immunosuppressive protein or peptide". The specification offers no definition or example of an immunosuppressive protein or peptide on page 10, lines 24-33. Lacking a definition of this term, one cannot determine the metes and bounds of the claim with regard to the identity of the protein or peptide.

- Claim 89 appears to be indefinite because of the recitation of the cleavage site, "XhoI/XhoI". Clarification is requested about the identity of the XhoI/XhoI cleavage site.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74, 75, 79, 80-85 and 92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing antigenicity of adeno-associated virus (AAV) comprising modifying the capsid (VP), does not reasonably provide enablement for reducing antigenicity of AAV comprising the modification of any structural protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The breadth of the claims encompasses the modification of any structural protein of AAV that results in reduced antigenicity. The nature of the invention is the reduction of the antigenicity of AAV so that AAV can function as a vector for transformation of a cell (or in gene therapy) without inducing an immune response that attacks the vector. The state of the art is that the capsid protein of any virus, including AAV, is the outermost component, and therefore the first antigenic component that the immune system recognizes. Modifications to other structural proteins, such as those within the virus (nucleocapsid, for example), would not be expected to be recognized by the immune system until it has been processed and presented by antigen presenting cells. The effect of modifying structural proteins other than the capsid is not apparent

from the specification. There is no guidance on modifying other structural proteins, as evidenced by the specification on page 7, lines 18-24, which discloses that the modification may be present in the VP1, VP2 and/or VP3 structural protein(s). There are no working examples of modifications to non-capsid structural proteins. The level of skill in the art is high with regard to expected results from modifying capsid proteins of viruses, while the level of predictability is low regarding the modification of non-capsid structural proteins and the expected reduced immune response. Therefore, given the breadth of the claims, the state of the art, the lack of guidance in the specification, the lack of working examples, the high level of skill in the art, and the low level of predictability in the art, the claims are only enabled for modification of the VP proteins, but not the modification of non-capsid structural proteins.

Claim Rejections - 35 USC § 102

5. Claims 74-93 are rejected under 35 U.S.C. 102(b) as being anticipated by Mamounas *et al.* (WO 97/38723, herein, "Mamounas"). The claims are drawn to a method for reducing the antigenicity of AAV comprising using a structural protein of AAV that has been modified in such a way as to bring about reduction in the antigenicity of AAV virus. The modification brings about a negligible reduction in the infectivity of the virus. The structural protein is capable of particle formation, and can be VP1, VP2 or VP3. The AAV can be AAV types 1-6, or any other AAV serotypes derived from AAV1-6. Specifically, the modification occurs on the surface of the virus, more specifically, at the N terminus of the structural protein. Also claimed for use in the method is a modified structural protein of AAV having an additional modification. According to the specification, a modification can be a covalent or non-covalent linkage of a

molecule to an amino acid or sequence (page 9, first full paragraph). A modification can also be a mutation in the amino acid sequence of the structural protein (page 9, second full paragraph). A modification can also be an insertion into the protein (page 10, lines 4-10). Proteins/peptides to be inserted include immunosuppressive proteins/peptides. The insertions occur in the XhoI cleavage site or in the BsrBI cleavage site of the VP1-encoding nucleic acid. When the modification is a deletion, it occurs between the XhoI or BsrBI/HindII cleavage sites of the VP-1 encoding nucleic acid. Also claimed are specific amino acid insertions located within the VP3 region (SEQ ID NOs: 2-9).

Mamounas discloses a capsid protein (structural protein) of AAV-2 that has been deleted (modified) in the VP1 or VP3 region (Example 1, pages 60-61, bridging paragraph, and page 67, part C). The deletion results in reduced specificity of the virus for the AAV receptor (page 4, lines 22-26), which is a reduction of the antigenicity of the virus for its natural receptor. Mamounas modifications of the VP1, VP2 and VP3 genes include the end of the AAV capsid gene open reading frame, and the start codon of the individual capsid genes (page 67, lines 13-22). Anti-CD34 scFv sequence was ligated to the 5' end of the VP1, VP2, and VP3 sequences using HindIII and NotI sites (page 67, lines 21-26). Some of the insertions occur in the XhoI and XbaI cleavage sites (page 67, lines 21-23). Mamounas also teaches deleting a region of the VP1 or VP3 region and inserting a targeting ligand, which is an additional modification (page 4, lines 28-31). Antibodies, such as single chain variable region fragments, biotin, poly-L-lysine, transferrin, and other proteins are contemplated by Mamounas for integration into the VP regions (pages 30-32). These proteins can be considered high or low molecular weight compounds. Lacking a definition of an "immunosuppressive protein or peptide" in claim 83, the proteins and

peptides taught by Mamounas meet the limitation. Mamounas does not explicitly say that the insertion occurs between the BsrBI/HindII cleavage sites of the VP-1 encoding nucleic acid, however, since insertions occurred in the XhoI cleavage site, the insertions would be expected to take place somewhere within the BsrBI/HindII cleavage site because BsrBI/HindII cleavage sites are within the XhoI cleavage site. Regarding claim 91, which has the limitation of specific locations of insertions in VP3, the claims only require that the insertion be located before and/or after at least one amino acid in a sequence. Given that the claims only require that the insertion be before or after an amino acid, one would expect that the insertions by Mamounas would have occurred before or after an amino acid. Therefore, the claims are anticipated by Mamounas.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily drawn to the following:

- Applicant argues that Mamounas' AAV vector's structural protein is incapable of supporting viral particle formation. Applicant points to pages 67-68, where Mamounas discloses that an antibody-AAV construct (scFc-AAV capsid chimera) failed to produce any intact viral particles. Applicant argues that since Mamounas had to use a triple plasmid strategy to get intact viral particles, that Mamounas fails to teach the claimed invention.
    - In response, Applicant is arguing about limitations that are not in the claims. Specifically, the claims are not limited to a method that results in an intact viral particle that is accomplished *only* by the recited steps of introducing a modification. Since the method using the term, "comprising", the method is open-ended and includes any number of additional steps. Mamounas' method

does what Applicant's method does, with the additional steps of a triple-plasmid strategy in order to get an intact particle. Mamounas' method results in the same product, but with additional steps. The open claim language does not preclude the steps taken by Mamounas.

- Applicant argues that Mamounas does not teach the reduction in antigenicity of the virus relative to wild-type AAV.
  - In response, Applicant is arguing about limitations that are not present in the claims. The claims do not specify what specific reduction in antigenicity is required. Mamounas teaches reduced specificity of the virus for the natural virus receptor. Reduced specificity qualifies as reduced antigenicity.
- Applicant argues that Mamounas does not teach the negligible reduction in viral infectivity.
  - In response, since Applicant has not adequately defined the level of reduction in viral infectivity that is "negligible", Mamounas' vector meets the limitation of the claims. (See the rejection of claims 74-93 under 35 U.S.C. 112, second paragraph.)

Conclusion

6. No claim is allowed. Applicant's amendment (adding 20 new claims and canceling all prior pending claims) necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

SBC

Stacy B. Chen
April 6, 2005

James C. Housel 4/16/05